Remarks

Claims 66-73, 89 and 90 were pending in the subject application. By this amendment, applicants canceled claims 66-73 and 89 without disclaimer or prejudice, amended claim 90 and added new claim 91. Accordingly, claims 90 and 91 are pending and under examination upon entry of this response.

Support for amended claim 90 can be found, *inter alia*, on page 8, lines 18-21; on page 29, lines 25-28; on page 81, line 31 to page 82, line 2; and on page 82, lines 20-23 of the subject application.

Support for new claim 91 can be found, *inter alia*, on page 7, lines 28-30; on page 8, lines 1-7 and lines 18-21;on page 8, lines 16 to page 9, line 9; on page 27, lines 17-20; on page 29, lines 25-28; on page 81, line 31 to page 82, line 2; on page 82, lines 20-23

Priority

In the April 19, 2007 Office Action, the Examiner granted effective filing date of April 21, 1989 for the subject matter in claims 66-68, 70 and 89-90 based of the filing date of U.S. Serial No. 07/341,436. The subject matter of new claim 91 is also entitled to the April 21, 1989 effective filing date.

Pursuant to M.P.E.P. §211.11(G) applicants have deleted the claim to benefit of application filed earlier than U.S. Serial No. 07/341,436, filed April 21, 1989.

Rejection of claims 66-73 and 89 are Now Moot

The Examiner rejected claims 66-70 and 89 under 35 U.S.C. §101, as allegedly directed to non-statutory subject matter. Since claims 66-70 and 89 have been canceled, this rejection is moot.

The Examiner rejected claims 66-68, 70 and 89 under 35 U.S.C. §102(b) as allegedly anticipated by the Physician's Desk Reference (PDR:1985) pages 1811-13; Griffith I (Griffith et al., Ann. Surg. 196(9/82):324-329) or Griffith II (Griffith et al., J. Thorac. Cardiovasc. Surg. 99 (12/84):952-957) as evidenced by Holschermann et al., Circulation 96 (12/97) 4232-4238. Since claims 66-68, 70 and 89 have been canceled, this rejection is moot.

The Examiner rejected claims 66-67, 69 and 70 under 35 U.S.C. §102(b) as allegedly anticipated by Gerscher et al. or Hunter et al. Since claims 66-67, 69 and 70 have been canceled, this rejection is moot.

The Examiner rejected claims 71-72 under 35 U.S.C. §102(b) as allegedly anticipated by Pasleau et al. Since claims 71-72 have been canceled, this rejection is moot.

The Examiner rejected claims 71-73 under 35 U.S.C. §102(b) as allegedly anticipated by Cullen. Since claims 71-73 have been canceled, this rejection is moot.

The Examiner provisionally rejected claims 66-71 under 35 U.S.C. §101 as allegedly claiming the same invention as that of claims 66-73 of copending Application No. 10/037,415. Since claims 66-73 have been canceled, this rejection is moot.

The Examiner rejected claims 66-68, 70 and 89 on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-5, 9-17, 20-63, 88-176 and 192-203 of U.S. Patent No. 6,410,516. Since claims 66-68, 70 and 89 have been canceled, this rejection is moot.

REJECTIONS OF CLAIM 90

Rejection under 35 U.S.C. §101

In the April 19, 2007 Office Action, the Examiner rejected claim 90 under 35 U.S. C. § 101 as allegedly directed to non-statutory subject matter. The Examiner alleged that the levels and activity of NF-κB are regulated (increased or decreased) by normal metabolic processes and the function of NF-κB to act as an intracellular messenger to transmit signals that induce expression of target genes is likewise a natural process in cells of the human body. The Examiner alleged that "the instant claims therefore read on naturally occurring phenomena which do not recite, or require, the hand of man."

Applicants' Response

In response, applicants have amended claim 90 to clarify the

invention. Accordingly, applicants respectfully request the Examiner to reconsider and withdraw the rejection of claim 90 under 35 U.S.C. §101.

Rejection under 35 U.S.C. §102(b)

In the April 19, 2007 Office Action, the Examiner rejected claim 90 under 35 U.S.C. §102(b) as allegedly anticipated by the Physician's Desk Reference (PDR:1985) pages 1811-13; Griffith I (Griffith et al., Ann. Surg. 196(9/82):324-329) or Griffith II (Griffith et al., J. Thorac. Cardiovasc. Surg. 99 (12/84):952-957) as evidenced by Holschermann et al., Circulation 96 (12/97) 4232-4238. The Examiner alleged that the conflicting claims are inherently anticipated by the prior art.

Specifically, the Examiner alleged that PDR(1985), Griffith (I) and Griffith (II) "teach administration of cyclosporine A (CsA) to (into) cells in the cardiac patients, which is shown from the teachings of Holschermann to inherently regulate (reduce) NF-κB activity and this would inhibit (reduce) expression of genes whose transcription is regulated by NF-κB activity."

In this matter, the applicants' respectfully traverse.

On page 6 of the April 19, 2007 Office Action, the Examiner alleges that Holschermann et al. provides extrinsic evidence that the PDR 1985, Griffith et al. I and Griffith et al. II references inherently anticipate the subject. Further, the

Examiner alleges that Holschermann et al. "essentially repeated the tests disclosed in the Griffith I and II references by administering 3.4 + 0.3mg/kg/day CsA to cardiac transplant patients, resulting in blood levels of 681 + 176 ng/ml." The applicants respectfully traverse. Holschermann et al. did not "essentially" repeat the tests disclosed in Griffith et al. I and II. In this regard applicants direct the Examiner to the Declaration Under 37 C.F.R. § 1.132 of Dr. Inder Verma, attached as **Exhibit A**. As discussed in paragraphs 12 and 13 of the Declaration of Dr. Inder Verma, the protocol used by Holschermann et al. differs from the protocols used by Griffith et al. I and Griffith et al. II. Patients in the prior art studies did not receive the same drug cocktail as those in Holschermann et al. and therefore it is unclear what effect, if any, CsA had on the patients. One skilled in the art would expect a cocktail of different active drugs, as described, to result in different patient outcomes. Certainly one skilled in the art would not understand results of a different protocol to explain what inherently happened in the prior art.

Further, the PDR 1985 provides dosage and administration instructions for the use of CsA and discloses a specific protocol of administration: "the initial does of Sandimmune (cyclosporine) Oral Solution should be given 4-12 hours prior to transplantation..." (emphasis added, page 1813, first column). Likewise, the timing of administration of the drug cocktails differs between the prior art and Holschermann et al. as discussed in paragraph 13 of the Declaration of Dr. Inder Verma.

Holschermann et al. do not begin CsA treatment until 3 to 4 days after surgery, a highly relevant departure from the studies described in the prior art. Therefore, not only does the prior art disclose pretreatment of subjects with CsA, but Holschermann et al. cannot be used to explain what occurred in the prior art.

Further, on pages 6-7 of the April 19, 2007 Office Action, the Examiner alleged that Holschermann et al. "confirms that administering CsA to cardiac patients as taught by the prior art PDR 1985 and Griffith I and II references necessarily inherently reduces NF-κB activity (and binding of NF-κB to NF-κB recognition sites)." Specifically, the Examiner asserted that "In cells obtained from transplant recipient during low baseline CsA blood levels (before CsA administration), strong NF-κB binding activity was detected (Fig. 4), whereas cells separated from blood in the presence of high CsA concentrations exhibited decisively reduced NF-KB biding activity." The Examiner contends that "Holshermann also showed that the administration of CsA to these patients as taught in the prior art PDR 1985 and Griffith I and II references reduced Tissue Factor (TF) gene transcription, which is recognized as being regulated by NF-κB:"Indeed, the marked activation of the NF-κB transcription factor, which is known to play a major role in the regulation of the TF gene, was prevented in the presence of high CsA blood concentrations." Id. At 4237."

The applicants respectfully traverse.

As discussed in paragraphs 15 and 16 of the Declaration of Dr. Inder Verma and elaborated further below, Figures 3 and 4 of Holschermann et al., which the Examiner has pointed to in alleged confirmation of the ability of CsA to reduce the levels of a protein, tissue factor (TF) purported to be regulated by NF-κB, cannot demonstrate that the administration of CsA, as described by Holschermann et al., reduces expression of a gene that had been induced, as recited by claim 90.

First, in Figure 3, the sample loaded into lane 2, which is derived from blood collected from patients prior to the daily CsA administration has no detectable level of mRNA. Further, it is only after a six hour incubation that one can observe a faint TF mRNA band, as indicated in lane 3. Notably, the sample collected from a patient after CsA administration and incubated for 6 hours shows no reduction in band intensity as shown in lane 6. It is only when the sample is incubated with LPS for 6 hours, can a prominent band be observed in lane 4, indicating an increase in TF mRNA transcription. These results demonstrate that the administration of CsA <u>prevented the induction</u> of TF mRNA by LPS as is indicated by the faint band in lane 7. Therefore, Figure 3 of Holschermann et al. shows that CsA cannot reduce existing TF transcription, though it appears to <u>prevent activation</u> of TF.

Likewise, comparision of these TF mRNA transcription results with those presented in Figure 4 demonstrate that CsA cannot reduce activated NF-κB. First, the samples depicted in the "prior to"

panel cannot correlate with a sample "prepared from blood mononuclear cells freshly isolated from transplant recipients before….CsA administration" (Figure 4, legend). If this were correct, Figure 3, lane 2, would depict the presence of TF mRNA, but it does not. The lack of activated TF mRNA, which is purported to be regulated by NF-κB, in samples obtained from patients prior to CsA administration indicates there is no activated NF-κB. The only conclusion that could correlate the results in Figure 3 to Figure 4 is that the samples obtained prior to CsA administration were incubated for 6 hours in the presence of LPS to stimulate NF-κB activity. In fact, in the legend for Table 2, such a step is described: "Mononuclear cell were isolated from peripheral blood samples of heart transplant recipients before and 4 hours after CsA administration, respectively, and assayed for TF activity after 6 hours of incubation with LPS" (page 4235). Therefore, the only interpretation that can reconcile the intense NF-κB bands observed in the "prior to" sample in Figure 4 with the results shown in Figure 3 is that the samples underwent the 6 hour incubation with LPS. Otherwise, the disconnect between the lack of TF transcription (Figure 3, lane 2) compared to intense NF-κB bands observed in the "prior to" samples in Figure 4 still exists. Since NF-κB has been shown to activate transcription of TF, the only reasonable explanation is the one provided above. Consequently, not only did Holschermann et al. not carry out the therapy protocols set forth in the prior art, but the data obtained by Holschermann et al. does not demonstrate that CsA

reduced expression of a gene that had been induced, as recited by claim 90.

Finally, as discussed in paragraph 17 of the Declaration of Dr. Inder Verma, the prior art references, PDR 1985, Griffith et al. I and Griffith et al. II do not provide enough detail to enable one of skill in the art to repeat their studies and arrive at the same results. The 1985 PDR provides dosage and administration instructions for the use of cyclosporine A. One of skill in the art would understand, that if one were to practice the method described in the 1985 PDR, one would observe a number of non-responsive patients or patients who exhibit adverse reactions (see table, page 1812). Therefore, the inherent variability in patient response to CsA and lack of access to the same patients populations used in these studies render it impossible for one to repeat the studies described in the prior art and obtain the same results. The 1985 PDR notes that "several study centers have found blood monitoring of cyclosporine useful in patient management" (page 1813, second column) and Griffith et al. II emphasizes this point, noting "the principal message is the lack of correlation between the dose of cyclosporine and the whole-blood level. Monitoring of the blood level in necessary to ensure that the administered dose provides a significant level of circulating cyclosporine" (page 954, first column). Thus, the lack of availability of the patient populations used in prior studies as well as the inherent variability in patients' responses to CsA would not enable one to practice the 1985 PDR, Griffith et al. I and Griffith et al. II studies and arrive at the same result.

Double Patenting

On page 12 of the April 19, 2007 Official Action, the Examiner provisionally rejected claim 90 under the doctrine of obviousness-type double patenting as unpatentable over claims 1-5, 9-17, 20-63, 88-176 and 192-203 of U.S. Patent No. 6,410,516. The Examiner alleged that the conflicting claims are not patently distinct from each other.

In response, applicants respectfully defer discussion of the provisional rejection until the obviousness-type double patenting rejection is the only rejection remaining in the present application. M.P.E.P. §804(I)(B)